REMARKS

Claims 22-26 are presented for examination. Applicants thank the Examiner for his review of the instant application. For the reasons stated below, the rejections of the presently pending claims are respectfully traversed.

Rejection Under 35 U.S.C. §101 – Utility

The Examiner maintains his rejection of pending Claims 22-26 under 35 U.S.C. § 101 as lacking utility. The PTO states that "The specification is entirely silent with regard to any utility for the PRO539 protein. ... While Applicant asserts that the PRO 539 protein shares the utility asserted for the PRO 539 nucleic acid as a diagnostic, that assertion is not supported by specific evidence of utility for PRO539 itself as being overexpressed in any cancer cell." *Office Action* at 3 (emphasis added).

Applicants note that the above statement is in error, as the specification states the following regarding Example 16:

> This example shows that the PRO1800-, PRO539-, PRO3434- and PRO1927-encoding genes are amplified in the genome of certain human lung, colon and/or breast cancers and/or cell lines. Amplification is associated with overexpression of the gene product, indicating that the polypeptides are useful targets for therapeutic intervention in certain cancers such as colon, lung, breast and other cancers and diagnostic determination of the presence of those cancers. *Specification* at 111-112 (emphasis added).

Clearly, the specification is not silent regarding a utility for PRO539, and the Examiner is requested to acknowledge that at a minimum, Applicants' have asserted a credible utility for the PRO539 polypeptide.

Applicants incorporate by reference their previously submitted arguments, and for the reasons of record assert that the specification contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented and therefore must be taken as sufficient to satisfy the utility requirement of 35 U.S.C. § 101. Applicants address each of the Examiner's arguments presented in the pending Office Action.

Duty of the Examiner in Examination of an Application

Applicants respectfully remind the Examiner that he has a duty to consider and respond to Applicants' arguments in an attempt to clarify the issues in dispute:

> The examiner should never lose sight of the fact that in every case the applicant is entitled to a full and fair hearing, and that a clear issue between applicant and examiner should be developed, if possible, before appeal. *M.P.E.P. §706.07* (emphasis added).

Applicants have attempted to respond to each of the Examiner's previous arguments, pointing out what the Applicants view as the factual errors or flaws in the Examiner's reasoning. Applicants respectfully request that the Examiner respond to Applicants' arguments in an attempt to clarify the issues in dispute prior to appeal. As provided in the M.P.E.P.:

> It is essential for Office personnel to recognize, fully consider and respond to **each substantive element** of any response to a rejection based on lack of utility. Only where the totality of the record continues to show that the asserted utility is not specific, substantial, and credible should a rejection based on lack of utility be maintained. *M.P.E.P.* § 2107 (emphasis added).

The Examiner's Cited References are Not Relevant

Under the heading "Protein and DNA Microarray data shows no necessary correlation between mRNA overexpression and protein expression," the Examiner argues that seven out of eight microarray papers show discordant protein and mRNA expression data. Applicants respond to each of these seven references below.

a. Czupalla et al.

The Examiner repeats his argument that "[t]he data of Czupalla, which addresses 117 genes, shows that it is more likely than not in this data set that there is no correlation between mRNA expression and protein expression. This supports the conclusion that mRNA expression cannot be relied upon for enablement and utility of the protein since no necessary correlation exists." *Office Action* at 4.

In response to the Examiner's reliance on Czupalla, Applicants offered the following arguments in their previous response:

> As the PTO notes, the authors report finding two groups of proteins: those where there is a change in mRNA with a corresponding change in protein, and those

> where there is a change in protein and no change in mRNA. As discussed above, and previously, Applicants are not concerned with predicting mRNA levels from changes in protein, and therefore a lack of correlation in the second group is irrelevant. ... Only three of the 47 genes from the first group are mentioned as having discordant mRNA and protein changes. Apparently, the other 44 genes, or 94%, showing a change in mRNA had a corresponding change in protein. Therefore, rather than supporting a lack of correlation between changes in mRNA leading to changes in protein, Czupalla actually strongly supports Applicants' position. *Response dated October 18, 2006* at 13-14 (citations omitted).

In response to Applicants' thorough review of Czupalla, the Examiner responds by summarily stating:

> Applicant then attacks a variety of the microarray references of Czupalla, Chen, Ginestier, Washburn, Anderson, Conrad and Kwong. All of Applicant's arguments are essentially spurious. Applicant does not rebut the basic factual point that each of these references support, which is that when large numbers of proteins are analyzed for expression alongside large numbers of nucleic acids, there is no correlation in expression. This result is repeated in essentially every large scale study cited and is true in additional uncited studies. The data is clear. *Office Action* at 29 (emphasis added).

The Examiner's response is insufficient as it does not address the substance of Applicants' arguments. Merely comparing large numbers of proteins alongside large numbers of nucleic acids and finding no correlation is not sufficient to rebut Applicants' assertions if the comparisons relied on are not relevant. In addition, the Examiner cannot rely on "uncited studies" that are not of record. Applicants request that the Examiner explain how Applicants' arguments repeated above are "essentially spurious," and make of record any "uncited studies" relied on by the Examiner. Applicants have made a factually and logically sound argument that explains why Czupalla does not support the Examiner's rejection of Applicants' asserted utility. Specifically, Applicants request that the Examiner respond to the following arguments regarding Czupalla: 1.) data reporting a change in protein expression without a change in mRNA expression is not relevant in determining whether a change in mRNA expression results in a change in protein expression; and 2.) the remaining data in Czupalla supports Applicants' assertion because, apparently, 94% of the genes showing a change in mRNA had a corresponding change in protein.

Contrary to the Examiner's assertion that "Applicant does not rebut the basic factual point that each of these references support," Applicants have addressed the data presented by

Czupalla and explained why they are either not relevant or actually support Applicants' position. The Examiner cannot continue to rely on a reference which reports a lack of correlation if the reported lack of correlation is not relevant to Applicants' assertions. It is the responsibility of the Examiner to address Applicants' arguments, and explain why they are factually or logically flawed.

Applicants invite the Examiner to either explain how Applicants' analysis of Czupalla is flawed, or acknowledge that Applicants' analysis is correct and state for the record that he is no longer relying on Czupalla. Doing so would clarify the issues in dispute for appeal. Summarily dismissing Applicants' arguments as "essentially spurious" is not sufficient. In addition, the Examiner is required to make of record any "uncited studies" relied on by the Examiner.

b. Kwong et al.

The Examiner repeats his statement that Kwong analyzed 47 genes in colorectal cancer, and that:

> "Only 12 of 47 genes exhibited correlated expression at a significance level less than 0.05. Surprisingly, 13 genes had a negative correlation between mRNA and protein levels. The correlation between protein and mRNA was also compared on a sample-by-sample basis. Of the 53 samples for which data was available, mRNA and protein levels were found to be correlated at a significance level of 0.05 in only 14 samples, while 14 mRNA and proteins were negatively correlated." Following Kwong, it is clear that it is not more likely than not that protein and mRNA expression are correlated. In fact, Kwong supports the conclusion that it is more likely than not that there is no correlation. *Office Action* at 4-5 (citations omitted).

In response to the Examiner's reliance on Kwong, Applicants offered a detailed explanation of why the first set of experiments from Kwong relied on by the Examiner are not relevant: Kwong did not examine genes which were differentially expressed, and therefore does not address the issue of whether differential mRNA expression leads to differential protein expression. As for the second portion of Kwong, Applicants have offered several arguments and illustrations to demonstrate why references such as Kwong that rely on a global ratio common between all steady state mRNA levels and all steady state protein levels are not relevant to Applicants' assertions regarding differential mRNA expression of a particular gene leading to

differential expression of the encoded protein. Applicants direct the Examiner's attention to pages 14-16, and 20-21 of the previous response.

In response to Applicants' arguments, the Examiner responds by summarily stating:

> Applicant then attacks a variety of the microarray references of Czupalla, Chen, Ginestier, Washburn, Anderson, Conrad and Kwong. All of Applicant's arguments are essentially spurious. Applicant does not rebut the basic factual point that each of these references support, which is that when large numbers of proteins are analyzed for expression alongside large numbers of nucleic acids, there is no correlation in expression. *Office Action* at 29 (emphasis added).

The Examiner's response is insufficient as it does not address the substance of Applicants' arguments. Merely comparing large numbers of proteins alongside large numbers of nucleic acids and finding no correlation is not sufficient to rebut Applicants' assertions if the comparisons relied on are not relevant. Applicants request that the Examiner explain how Applicants' analysis of Kwong summarized above is "essentially spurious." Specifically, Applicants request that the Examiner respond to the following arguments regarding Kwong: 1.) data examining a correlation between mRNA and protein expression where there is no change in mRNA expression is not relevant in determining whether differential mRNA expression results in differential protein expression; and 2.) references such as Kwong that examine a correlation between mRNA and protein expression across different genes are not relevant to Applicants' assertions regarding differential mRNA expression for a particular gene leading to differential expression of the encoded protein. It is the responsibility of the Examiner to address Applicants' arguments, and explain why they are factually or logically flawed.

Applicants invite the Examiner to either explain how Applicants' analysis of Kwong is flawed, or acknowledge that Applicants' analysis is correct and state for the record that he is no longer relying on Kwong. Doing so would clarify the issues in dispute for appeal. Summarily dismissing Applicants' arguments as "essentially spurious" is not sufficient.

c. Chen et al.

The Examiner repeats his citation of Chen: "By comparing the mRNA and protein expression levels within the same tumor samples, we found that 17% (28/165) of the protein spots (21/98 genes) show a statistically significant correlation between mRNA and protein. ... The majority of protein isoforms, however, did not correlate with mRNA levels and thus their

expression is regulated by other mechanisms. We also observed a subset of proteins that demonstrated a negative correlation with the mRNA expression values." *Office Action* at 5.

In response, Applicants offered a careful review of the data underlying Chen's statements, and explained why Applicants view Chen as not relevant to determining if Applicants' asserted utility is more likely than not true. Applicants direct the Examiner's attention to pages 16-18 of Applicants' response. Briefly stated, Chen's global analysis is not relevant for the reasons discussed with respect to Kwong and similar references. As for the portions of Chen cited by the Examiner, Applicants argued that the only data reported by Chen which shows substantial changes in the expression of mRNA, Figures 2A-C, supports Applicants' assertion that substantial changes in mRNA levels will correspond to substantial changes in polypeptide expression since a correlation was observed. As for the lack of an observed correlation between mRNA levels and protein levels for other genes reported by Chen, no conclusion can be drawn since there is no indication the genes are differentially expressed. Thus, Chen's results do not refute Applicants' position. If anything, Chen supports Applicants' position that a significant correlation exists between changes in mRNA and changes in the encoded protein level.

In response to Applicants' arguments, the Examiner responds by summarily stating:

> Applicant then attacks a variety of the microarray references of Czupalla, Chen, Ginestier, Washburn, Anderson, Conrad and Kwong. All of Applicant's arguments are essentially spurious. Applicant does not rebut the basic factual point that each of these references support, which is that when large numbers of proteins are analyzed for expression alongside large numbers of nucleic acids, there is no correlation in expression. This result is repeated in essentially every large scale study cited and is true in additional uncited studies. The data is clear. To reiterate just one of the papers, Chen notes "By comparing the mRNA and protein expression levels within the same tumor samples, we found that 17% (28/165) of the protein spots (21/98 genes) show a statistically significant correlation between mRNA and protein." Chen continues a little later "The majority of protein isoforms, however, did not correlate with mRNA levels and thus their expression is regulated by other mechanisms. We also observed a subset of proteins that demonstrated a negative correlation with the mRNA expression values." *Office Action* at 29-30 (emphasis added).

The Examiner's response is insufficient as it does not address the substance of Applicants' arguments. The Examiner's response is without any substance as it merely repeats the same arguments previously made regarding Chen. Applicants have addressed these statements at length in the previous response, and request that the Examiner explain how

Applicants' analysis of Chen summarized above is "essentially spurious." Specifically, Applicants request that the Examiner respond to the following arguments regarding Chen: 1.) references such as Kwong and portions of Chen that examine a correlation between mRNA and protein expression across different genes are not relevant to Applicants' assertions; and 2.) data examining a correlation between mRNA and protein expression where there is no change in mRNA expression are not relevant in determining whether a change in mRNA expression results in a change in protein expression. It is the responsibility of the Examiner to address Applicants' arguments, and explain why they are factually or logically flawed.

Applicants invite the Examiner to either explain how Applicants' analysis of Chen is flawed, or acknowledge that Applicants' analysis is correct and state for the record that he is no longer relying on Chen. Doing so would clarify the issues in dispute for appeal. Summarily dismissing Applicants' arguments as "essentially spurious" is not sufficient.

d. Conrad et al.

The Examiner continues to rely on Conrad, asserting that comparing the abundance of protein to nucleic acid microarray for proteins, Conrad reported "There is little correlation between RNA and protein abundance identified and predicted by cICAT." *Office Action* at 5.

As Applicants stated in their previous response at pages 18 and 20-21, the Examiner's reliance on Conrad is misplaced for the same reason that the second portion of Kwong is not relevant to Applicants' assertion: the authors of Conrad plotted a single time point for mRNA against a single time point for protein expression, looking for a correlation across the ~1900 genes. The only way this analysis will result in a significant correlation is if the ratio of mRNA:protein is constant across all ~1900 genes. Whether genes share a common mRNA:protein ratio or not is irrelevant because this type of experiment cannot address whether differential mRNA expression for a single gene generally results in differential protein expression for the corresponding protein – the two issues are independent of each other.

In response to Applicants' arguments, the Examiner responds by summarily stating:

> Applicant then attacks a variety of the microarray references of Czupalla, Chen, Ginestier, Washburn, Anderson, Conrad and Kwong. All of Applicant's arguments are essentially spurious. Applicant does not rebut the basic factual point that each of these references support, which is that when large numbers of

> proteins are analyzed for expression alongside large numbers of nucleic acids, there is no correlation in expression. *Office Action* at 29 (emphasis added).

The Examiner's response is insufficient as it does not address the substance of Applicants' arguments as discussed above with respect to Czupalla, Kwong, and Chen. Applicants request that the Examiner explain how Applicants' analysis of Conrad summarized above is "essentially spurious." Specifically, Applicants request that the Examiner respond to the following argument regarding Conrad: references such as Kwong, portions of Chen, and Conrad that examine a correlation between mRNA and protein expression across different genes are not relevant to Applicants' assertions regarding changes in mRNA level for a particular gene leading to changes in the level of the encoded protein. It is the responsibility of the Examiner to address Applicants' arguments, and explain why they are factually or logically flawed.

Applicants invite the Examiner to either explain how Applicants' analysis of Conrad is flawed, or acknowledge that Applicants' analysis is correct and state for the record that he is no longer relying on Conrad. Doing so would clarify the issues in dispute for appeal. Summarily dismissing Applicants' arguments as "essentially spurious" is not sufficient.

e. Ginestier et al.

The Examiner continues to rely on Ginestier, stating that table 4 teaches that only 5 of 15 genes showed concordance, and that the authors report that "For a category of molecules we found important differences between RNA and protein expression levels." *Office Action* at 5.

Applicants previously noted that the Ginestier reference is difficult to interpret given the way the mRNA and protein samples were analyzed. Applicants also noted that Ginestier's analysis ignores the fact that in many cases, a relationship between mRNA and protein was not found because there were more samples with a "high" (class 3) protein expression level than there were samples with a "high" (class 3) mRNA level. As stated numerous times, this is not contrary to Applicants' assertion, as Applicants are not arguing that "high" protein levels are always and only due to "high" mRNA expression. In addition, the assignment of the protein and mRNA expression levels to class 1, 2, or 3 was arbitrary, and influences whether a relationship is seen or not. These flaws, combined with the fact that Ginestier was not looking at differential mRNA expression (*i.e.* a change in mRNA between condition X and condition Y), make

Ginestier of little value in assessing whether one of skill in the art would believe Applicants' assertions regarding differential mRNA expression leading to differential protein expression.

The Examiner's only response is that which is repeated above:

> Applicant then attacks a variety of the microarray references of Czupalla, Chen, Ginestier, Washburn, Anderson, Conrad and Kwong. All of Applicant's arguments are essentially spurious. Applicant does not rebut the basic factual point that each of these references support, which is that when large numbers of proteins are analyzed for expression alongside large numbers of nucleic acids, there is no correlation in expression. *Office Action* at 29 (emphasis added).

The Examiner's response is insufficient as it does not address the substance of Applicants' arguments as discussed above with respect to Ginestier. Applicants request that the Examiner explain how Applicants' analysis of Ginestier summarized above is "essentially spurious." Specifically, Applicants request that the Examiner respond to the following argument regarding Ginestier : 1.) data reporting a change in protein expression without a change in mRNA expression is not relevant in determining whether a change in mRNA expression results in a change in protein expression; and 2.) data examining a correlation between mRNA and protein expression where there is no change in mRNA expression is not relevant in determining whether a change in mRNA expression results in a change in protein expression. It is the responsibility of the Examiner to address Applicants' arguments, and explain why they are factually or logically flawed.

Applicants invite the Examiner to either explain how Applicants' analysis of Ginestier is flawed, or acknowledge that Applicants' analysis is correct and state for the record that he is no longer relying on Ginestier. Doing so would clarify the issues in dispute for appeal. Summarily dismissing Applicants' arguments as "essentially spurious" is not sufficient.

f. Anderson and Seilhamer

The Examiner repeats his previous argument that "Anderson et al shows that for 19 proteins that were compared between 20 gel electrophoresis and mRNA analysis 'the correlation coefficient obtained over this set of data was 0.48. This number is intriguingly close to the middle position between a perfect correlation (1.0) and no correlation whatever (0.0).' In fact, the correlation is slightlycloser to showing that there is no correlation whatsoever between protein and mRNA data." *Office Action* at 6.

Applicants previously argued that like the second portion of Kwong, part of Chen, and Conrad, the Anderson paper is irrelevant because the authors examined the correlation between mRNA and protein across different genes – this is a search for a common global ratio of mRNA:protein. This is equivalent to conducting a hypothetical Experiment 1, where a particular cell type has 100 copies of mRNA for gene X, 200 copies of mRNA for gene Y, and 400 copies of mRNA for gene Z. If there is a common global ratio of mRNA:protein such that there is a correlation between mRNA levels and protein levels across genes, the relative amount of proteins X:Y:Z would be approximately 1:2:4 since this is the relative amount of their respective mRNAs. This is essentially what the cited references examined.

In contrast, Applicants are relying on a correlation between differential mRNA expression for a particular gene leading to corresponding differential expression of the encoded protein when comparing tissues at two different times or conditions. For example, in hypothetical Experiment 2, if gene X has 100 copies of mRNA per cell in condition A (*e.g.* normal), and 200 copies of mRNA for gene X in condition B (*e.g.* tumor), the amount of protein X in condition A would be smaller than the amount of protein X in condition B, for example, having a ratio of 1:2, such that there is a correlation between the difference in the level of mRNA and the difference in the level of protein for a particular gene.

By relying on Kwong, Chen, Conrad and Anderson, the Examiner is apparently arguing that because there is no correlation between levels of mRNA and protein across different genes in a particular sample, as illustrated by Experiment 1, one of skill in the art would not expect an increase or decrease in the amount of mRNA for a particular gene to result in a corresponding change in the amount of the encoded protein, as illustrated in Experiment 2. This is simply wrong – there does not need to be a global ratio of mRNA:protein across genes for there to be a correlation in changes of mRNA and protein for a particular gene.

Applicants also offered an analogy to gas mileage in different types of automobiles to illustrate and clarify the flaw in the Examiner's position on this point.

Instead of addressing the substance of these arguments and illustrations, the Examiner summarily dismissed them by stating:

> Applicant then attacks a variety of the microarray references of Czupalla, Chen, Ginestier, Washburn, Anderson, Conrad and Kwong. All of Applicant's arguments are essentially spurious. Applicant does not rebut the basic factual

> point that each of these references support, which is that when large numbers of proteins are analyzed for expression alongside large numbers of nucleic acids, there is no correlation in expression. *Office Action* at 29 (emphasis added).

The Examiner's response is insufficient as it does not address the substance of Applicants' arguments as discussed above with respect to Czupalla, Kwong, Chen and Anderson. Applicants request that the Examiner explain how Applicants' analysis of Anderson summarized above is "essentially spurious." Specifically, Applicants request that the Examiner respond to the following argument regarding Anderson: references such as Kwong, portions of Chen, Conrad and Anderson that examine a correlation between mRNA and protein expression across different genes are not relevant to Applicants' assertions regarding differential mRNA expression for a particular gene leading to differential expression of the encoded protein. It is the responsibility of the Examiner to address Applicants' arguments, and explain why they are factually or logically flawed.

Applicants invite the Examiner to either explain how Applicants' analysis of Anderson is flawed, or acknowledge that Applicants' analysis is correct and state for the record that he is no longer relying on Anderson. Doing so would clarify the issues in dispute for appeal. Summarily dismissing Applicants' arguments as "essentially spurious" is not sufficient.

g. Washburn et al.

The Examiner also continues to rely on Washburn, which the Examiner asserts discloses a correlation of 0.45 when examining 678 loci. *Office Action* at 6. The Examiner concludes that this is closer to the absence of a correlation than to a positive correlation. *Id.*

Applicants have acknowledged that the authors of Washburn conducted an experiment which more directly addresses Applicants' assertion because the authors of Washburn looked at the relationship between changes in mRNA and protein expression in yeast grown in minimal and rich media. The authors plotted the log of the ratio of mRNA expression in minimal and rich media against the log of the ratio of protein expression in minimal and rich media. The authors report a weak (0.45) correlation.

However, the authors note that "[a] majority of the data points deviating from the perfect positive correlation line shown fall on the y axis indicating that more loci had altered protein expression and unchanged mRNA expression than loci having altered mRNA expression and

unchanged protein expression." *Washburn* at 3109 column 1. In fact, looking at Figure 2, if the data points for loci where the mRNA levels did not change by at least two-fold are eliminated (*i.e.*, values between -1 and 1), it appears that there would be an excellent correlation between the changes in mRNA and the changes in protein. As Applicants' have previously stated, changes in protein level without changes in mRNA are not relevant to Applicants' assertion. The question is whether an increase in mRNA generally results in a change in protein. Based on the data in Washburn, the answer appears to be "yes." Thus, Washburn is not contrary to Applicants' assertion, but rather supports it.

Again, the Examiner has offered no rebuttal to Applicants' analysis and arguments concerning Washburn:

> Applicant then attacks a variety of the microarray references of Czupalla, Chen, Ginestier, Washburn, Anderson, Conrad and Kwong. All of Applicant's arguments are essentially spurious. Applicant does not rebut the basic factual point that each of these references support, which is that when large numbers of proteins are analyzed for expression alongside large numbers of nucleic acids, there is no correlation in expression. *Office Action* at 29 (emphasis added).

The Examiner's response is insufficient as it does not address the substance of Applicants' arguments. The Examiner has cited Washburn as a reference which supports his position, when in fact it supports Applicants'. Applicants request that the Examiner respond to the following argument regarding Washburn: 1.) data reporting a change in protein expression without a change in mRNA expression is not relevant in determining whether a change in mRNA expression results in a change in protein expression; and 2.) the remaining data in Washburn supports Applicants' assertion because it appears that the vast majority of genes showing a change in mRNA had a corresponding change in protein. It is the responsibility of the Examiner to address Applicants' arguments, and explain why they are factually or logically flawed.

Applicants invite the Examiner to either explain how Applicants' analysis of Washburn is flawed, or acknowledge that Applicants' analysis is correct and state for the record that he is no longer relying on Washburn. Doing so would clarify the issues in dispute for appeal. Summarily dismissing Applicants' arguments as "essentially spurious" is not sufficient.

h. Conclusion – the references cited are not contrary to Applicants' assertion

The Examiner concludes his discussion of the above references by stating:

> Combining the data from Czupalla, Kwong, Orntoft, Chen and Ginestier, they analyzed 384 genes in total. There was a correlation between the RNA and protein levels for 131 of these genes .... This results in a final correlation of 34%, which means that it is more likely than not that there is no correlation between RNA and protein levels. So not only is there no necessary connection between the level of protein in a cell and the amount of mRNA, but there is also no necessary correlation between the amount of DNA in a cell and the amount of mRNA. Therefore, any evidence by Applicant showing overexpression of one component does not provide utility for the protein itself. *Office Action* at 6 (emphasis added).

This conclusion is flawed for several reasons.

First, it is flawed because the Examiner is relying on references and data that, for the reasons discussed above, simply are not relevant to Applicants' assertion, or support Applicants' position. The Examiner has provided no explanation as to why the references should be considered in light of Applicants' analysis and arguments. As stated in the M.P.E.P.:

> It is essential for Office personnel to recognize, fully consider and **respond to** each substantive element of any response to a rejection based on lack of utility. *M.P.E.P.* § 2107 (emphasis added).

Second, the Examiner's conclusion is flawed because the Examiner is impermissibly ignoring the numerous references cited by Applicants in their previous response – the Examiner must consider all the evidence of record, not just the evidence submitted by the Examiner. The Examiner has chosen to ignore Applicants' evidence, apparently because:

> None of these references...represents the sort of global comparison of many (as many as 2501) different proteins to their corresponding mRNAs that was performed by the microarray comparison papers cited in the action above. Applicant selectively chooses art to support one position, rather than attempting to balance all of the act and determine the consensus of opinion. In the utility analysis, all of the microarray papers, including the Polakis data, were analyzed in a combined fashion, where the raw data was available, in order to provide as objective an opinion as possible. Attempts to overload the examiner with prior art, particularly where all of the prior art does not even support the position taken (as will be discussed below), are not persuasive. *Office Action* at 28.

Applicants submit that this response illustrates that the Examiner is not performing his duty of evaluating all the evidence of record. If the Examiner is overloaded by references which support Applicants' position, but feels that these references are not representative of the

"consensus of opinion," it is the Examiner's responsibility to make the references which support this alleged "consensus of opinion" of record, and weigh them against Applicants' evidence. The Examiner cannot refuse to consider Applicants' evidence in favor of his own because he does not believe Applicants' evidence represents the "consensus of opinion." Applicants, (as well as the three experts whose declarations Applicants have submitted), disagree with the Examiner as to what the "consensus of opinion" regarding the issue at hand is, and Applicants have submitted references which support their position. Applicants invite the Examiner to cite to any authority – statute, case law, regulation, or M.P.E.P. – which allows the Examiner to ignore evidence of record because he disagrees with the conclusion such evidence supports.

Applicants submit that numerous references that examine one or a few genes in detail are at least as valuable as the "global comparisons" cited by the Examiner in determining whether or not a change in mRNA leads to a corresponding change in protein. If the Examiner feels that "global comparisons" are superior to Applicants' evidence, and therefore outweigh Applicants' evidence, the Examiner is obligated to explain why, including considering all of Applicants' evidence and responding to Applicants' arguments explaining why the Examiner's evidence is irrelevant. ("It is essential for Office personnel to recognize, **fully consider** and **respond to** each substantive element of any response to a rejection based on lack of utility." *M.P.E.P.* § 2107 (emphasis added)). A conclusory statement that "[t]his data is significantly superior to any presented by Applicant in rebuttal" will not suffice. *Office Action* at 30.

Third, the above conclusion is flawed because none of the references cited, other than Orntoft which found a strong correlation, examined the relationship between DNA and mRNA, and therefore there is no support in these references for the Examiner's conclusion that there is no correlation between DNA and RNA.

Finally, the conclusion is flawed because, as Applicants have repeatedly stated, the standard is not a "necessary" correlation, but merely a "reasonable" one.

As for the Examiner's assertion that not all of Applicants' cited references support Applicants' position, the Examiner offers the same three examples he previously submitted. *Office Action* at 30. Applicants have addressed these erroneous characterizations of Applicants' references. *See Response Mailed October 18, 2006,* at 30-31. Applicants invite the Examiner to either address Applicants' response, or withdraw his statements regarding Gromova, Aust, and

Kuo, and acknowledge that these references support Applicants' position. Doing so would clarify the issues in dispute for appeal.

The Meric, Gökman-Polar, and Pennica references do not constitute "Abundant Art" which is contrary to Applicants' Assertions

In addition to the references discussed above, the Examiner repeats his previous argument that "[a]bundant art supports the absence of a necessary relationship between mRNA and protein," citing Meric, Gökman-Polar, and Pennica. *Office Action* at 7-8 (emphasis added).

Applicants have previously discussed at length why the Meric, Gökman-Polar and Pennica references do not support the Examiner's position. Briefly stated, Applicants argue that Meric supports Applicants' assertion that generally, changes in mRNA lead to a corresponding change in the level of the encoded protein – that is why examining differences between tumor and normal tissue at the mRNA level is a "fundamental principle" of molecular cancer therapeutics. Likewise, Meric teaches that mRNA overexpression can be attributed to gene amplification. Gökman-Polar reports only that increased protein levels were not accompanied by increased mRNA levels – this is not contrary to Applicants' assertion that gene amplification leads to overexpression of an mRNA which leads to overexpression of the corresponding protein. In addition, Gökman-Polar reports a positive correlation between changes in mRNA level and changes in protein level for five of six samples tested. Finally, Pennica looked at a correlation between gene amplification and gene expression, not mRNA and protein, and reports one gene where there was a strong correlation between the two, and one possible example where there was a lack of positive correlation. This evidence is at best inconclusive, with at least half the genes showing a correlation between gene amplification and mRNA overexpression.

In response, the Examiner states:

> Applicant argues the Meric, Gokman-Polar, Pennica and Konopka references, by trying to argue, for example, that "Pennica et al has no teaching whatsoever about the correlation of mRNA expression and protein expression in general (see page 13 of response.) There is no doubt that each of these references are drawn to specific protein molecules. The references simply represent individual demonstrations of situations where proteins and mRNA are not correlated in abundance. Applicant attempts to rebut with other references which show the contrary fact pattern. *Office Action* at 28 (emphasis added).

This response does not address Applicants' arguments regarding the Meric, Gökman-Polar and Pennica references summarized above. In fact the quote attributed to Applicants in the Examiner's response isn't found on page 13 of Applicants' response, or on any other page for that matter. Applicants note that because Pennica in fact does not examine protein expression, it cannot support the Examiner's assertion that it "simply represent individual demonstrations of situations where proteins and mRNA are not correlated" or his conclusion that "[a]bundant art supports the absence of a necessary relationship between mRNA and protein." *Office Action* at 28 and 7. In addition, Applicants note that the Examiner is relying on references which allegedly "represent individual demonstrations of situations where proteins and mRNA are not correlated in abundance," the kind of reference the Examiner has criticized Applicants for submitting.

Applicants invite the Examiner to either explain how Applicants' analysis of Meric, Gokman-Polar, and Pennicais flawed, or acknowledge that Applicants' analysis is correct and state for the record that he is no longer relying on any of these references. Doing so would clarify the issues in dispute for appeal.

The PTO has Acknowledged that the Data Reporting Amplification of the PRO539 Gene is Sufficient to Provide Utility for the PRO539 Nucleic Acids as a Diagnostic Tools

Applicants next address the Examiner's argument that the evidence of amplification of the gene encoding the PRO539 polypeptide in lung and colon tumors is not sufficient to provide a substantial utility because "there is no showing that the overexpression was statistically significant" and because "there is no evidence that the overexpression was reproducible." *Office Action* at 8.

Applicants note that in the closely related application Serial No. 10/033,167, directed to nucleic acids related to SEQ ID NO:6 which encodes the PRO539 polypeptide, the PTO has acknowledged that the nucleic acids have utility. *See Notice of Allowability for Application 10/033,167 dated 7/21/2005.* Therefore, Applicants submit that the Examiner's rejection of the exact same data in the instant case based on the same arguments of alleged insufficient details are moot in light of the PTO's position in the related case.

In addition, as Applicants have previously stated, Applicants are not required to prove utility to a statistical certainty, only that it is more likely than not true. *See Nelson v. Bowler*, 626

F.2d 853, 856-57, 206 U.S.P.Q. 881, 883-84 (C.C.P.A. 1980) (reversing the Board and rejecting an argument that evidence of utility was insufficient because it was not statistically significant). As the M.P.E.P. states:

> [T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." **Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty**. Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. *M.P.E.P.* § 2107.02, part VII (bold emphasis added, underline in original, citations omitted).

Therefore, whether the results are statistically significant or not is irrelevant to establishing the asserted utility. The results must simply be reliable enough that one of skill in the art would believe that the utility is more likely than not true. Applicants request that the Examiner either support his requirement for statistical significance by citing to some authority, or acknowledge the correct standard cited by Applicants above and withdraw his arguments based on statistical significance. Doing so would clarify the issues in dispute for appeal.

Regarding reproducibility, the Examiner again **erroneously** states:

> Further, there is no evidence that the overexpression was reproducible. From the data presented in the specification, a single prostate tumor sample from a single patient may have been used. Such a result from a single patient would not support any utility because even if the nucleic acid was overexpressed in the one patient, there would be no expectation that the result would appear in even one other patient, so there is no evidence of record that the overexpression shown has any utility as a diagnostic or for any other purpose. Also, there is no evidence that the over expression in the prostate tumor was anything other than a nonspecific effect due to the presence of an exogenous protein in the mixture. *Office Action* at 8-9, (emphasis added).

As Applicants have previously pointed out, **THESE ARGUMENTS ARE MISPLACED AND IRRELEVANT, AS APPLICANTS' DATA DO NOT RELATE TO PROSTATE CANCER, BUT RATHER LUNG AND COLON CANCER**. As described in Example 16 of the present application, gene amplification of PRO539 in a variety of primary cancers and cancer cell lines was monitored using real-time quantitative TaqMan™ PCR. The gene amplification results are set forth in Table 7 (Table 8 as amended) on page 117 of the specification. As explained in the specification on page 112, lines 17-19, the results of TaqMan™ PCR are reported in ΔCt units. It is well-known in the art that "Ct" stands for "threshold cycle." One Ct unit corresponds to one PCR cycle or

approximately a 2-fold amplification, relative to control, 2 units correspond to 4-fold amplification, 3 units to 8-fold amplification, *etc.* *Specification* at 112, lines 17-19. Looking at the results reported on page 117, nine primary lung tumors and eight primary colon tumors were tested, as well as a number of tumor cell lines. PRO539 had a ΔCt value of greater than 1, *i.e.*, more than two-fold amplification, in six of nine lung tumors and five of eight colon tumors. Therefore, the Examiner's arguments regarding reproducibility are simply wrong.

Applicants request that the Examiner specifically withdraw this argument from the record since it is clearly based on a different application and is not relevant to the pending application. Doing so would clarify the issues in dispute for appeal.

Li et al., Ding et al., and Sawiris et al.

The Examiner repeats his argument that "the overwhelming state of the art supports the position that many genes are irrelevant, that genes whose expression does not change are noise, and that these irrelevant genes are so insignificant that ideally they are not placed on the arrays or used at all. The current gene, Pro539, is such a gene." *Office Action* at 9, citing Li, Ding, and Sawiris as support.

Again, this argument is moot because the PTO has already accepted that the PRO539 gene has utility as a diagnostic tool, as discussed above. In addition, the claims of the instant application are directed to antibodies to PRO539, not genes for use on gene expression arrays.

Applicants have explained at length why the three references cited do not support the Examiner's rejection of the asserted utility of using the PRO539 as a diagnostic agent for cancer. While the Examiner's statement that the prior art supports the conclusion that there are many irrelevant genes is not disputed, none of the references support the conclusion that the gene encoding PRO539 is one of those irrelevant genes when it comes to a diagnostic tool for cancer, particularly colon and lung cancer. As stated previously, the references indicate that the relevant genes are those that are overexpressed or underexpressed in the cancer of interest, genes like the one which encodes PRO539. Thus Applicants submit that the Examiner has failed to offer any support for his conclusion that PRO539 is not useful as a cancer diagnostic tool.

In response to Applicants' previous arguments regarding Li, Ding and Sawiris, the Examiner states:

> Li, Ding and Sawiris demonstrate that simple overexpression alone is insufficient to demonstrate association with disease. As noted above, only 143 out of 2000 genes in the comparison by Li of colon cancer with normal were identified as being useful in the diagnostic analysis of colon cancer. ... In the current case, there is no evidence that the overexpression has any diagnostic significance and there is ample evidence in the art of Li, Ding and Sawiris that overexpression alone, without further analysis, lacks diagnostic significance. *Office Action* at 26-27 (emphasis added).

This is not responsive to Applicants' arguments for at least two reasons. First, the evidence in the current case that the amplification of PRO539 has diagnostic significance is the fact that the PTO has issued a Notice of Allowability in the related case directed to PRO539 nucleic acids where Applicants asserted diagnostic utility for the claimed nucleic acids. Second, the Examiner has not pointed to any portion of the cited references to support his conclusion that "overexpression alone, without further analysis, lacks diagnostic significance." Applicants have previously addressed the portions of the cited references relied on by the Examiner. If the Examiner is relying on other portions of the cited references, Applicants invite the Examiner to draw them to Applicants' attention.

Absence of Tissue Matched Controls

The Examiner repeats his argument that the data regarding gene amplification of PRO539 are suspect because "tissue matched samples were not used as controls." *Office Action* at 10.

In response, Applicants previously noted that the Examiner has not explained why tissue matched controls are necessary to evaluate gene amplification in tumor samples, as opposed to gene overexpression where tissue matched controls may be necessary. In addition, the Examiner has yet to offer any support for its assertion that "both cancerous and non-cancerous lung tissue can be aneuploidy." *Id.* at 10. Even if he did, Applicants note that the PRO539 was amplified in colon tumors as well.

The Examiner has not responded to these arguments.

The Examiner's Response to Dr. Scott's Declaration Rests on Irrelevant Evidence

The Examiner has rejected Dr. Scott's declaration, based in large part on what the Examiner characterizes as "significant evidence which opposes the conclusion of the Scott declaration." *Office Action* at 18. The "significant evidence" is the Czupalla, Kwong, Chen, Ginestier, Conrad, Anderson, and Washburn references discussed above. *See Office Action* at 21. This "significant evidence" is irrelevant to determining whether changes in mRNA expression lead to changes in protein expression for a particular gene for the reasons discussed above – reasons which have yet to be addressed by the Examiner. In fact, Dr. Scott's declaration is supported by the overwhelming evidence submitted by Applicants.

As for the Examiner's statements regarding a comparison to "universal controls," rather than tissue matched controls, these arguments have been addressed by Applicants as discussed previously and above – a response which has yet to be addressed by the Examiner.

The Examiner's Legal Analysis is Flawed

The Examiner spends over four pages of his Office Action responding to Applicants' recitation of the legal standard for utility. Applicants disagree with the Examiner's statements, and will address what Applicants view as a flawed analysis in their Appeal Brief. Applicants note for the record that the Examiner bases his analysis on at least two factually inaccurate statements:

> "That is virtually identical to the current case, where Applicant argues that PRO539 is overexpressed along with 700 other molecules." *Office Action* at 24 (emphasis added);
>
> and
>
> "The only test data is represented by a single point in which the mRNA of PRO539 is stated to be overexpressed in a single lung tumor from a single patient without any statistical significance." *Office Action* at 25 (emphasis added).

These statements are clearly erroneous, and Applicant invites the Examiner to point to any portion of the application to support these statements. Applicants direct the Examiner to Example 16 of the instant application for a correct description of the data relied on for Applicants' asserted utility.

Utility – Conclusion

Applicants remind the Examiner that the evidence supporting utility does not need to be direct evidence, nor does it need to provide a "necessary" or an exact correlation between the submitted evidence and the asserted utility. Instead, evidence which is "reasonably" correlated with the asserted utility is sufficient. *See Fujikawa v. Wattanasin*, 93 F.3d 1559, 1565, 39 U.S.P.Q. 2d 1895 (Fed. Cir. 1996) ("a 'rigorous correlation' need not be shown in order to establish practical utility; 'reasonable correlation' suffices"); *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 U.S.P.Q. 739 (Fed. Cir. 1985) (same); *Nelson v. Bowler*, 626 F.2d 853, 857, 206 U.S.P.Q. 881 (C.C.P.A. 1980) (same). In addition, utility need only be shown to be "more likely than not true," not to a statistical certainty. *M.P.E.P.* at § 2107.02, part VII (2004). Considering the evidence **as a whole** in light of the relevant standards for establishing utility, Applicants have established at least one specific, substantial, and credible utility. In view of the above, Applicants respectfully request that the Examiner reconsider and withdraw the utility rejection under 35 U.S.C. §101.

Rejection under 35 U.S.C. §112 – Enablement

The Examiner also rejects Claims 22-26 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. The Examiner cites *In re Wands* and the factors set forth therein to determine the scope of enablement. The Examiner's arguments are largely the same as those for the utility rejection. *Office Action* at 12-16. In particular, the Examiner argues under the "unpredictability of the art and state of the art" heading that there is no "necessary" correlation between gene amplification and mRNA levels, or between mRNA and protein levels, citing the same references relied on for the utility rejection. *Office Action* at 13-15.

For the reasons of record, Applicants submit that the claimed antibodies are enabled, as one of skill in the art would know how to make and use them. Applicants submit that the evidence, declarations, references, and arguments discussed above make clear that Applicants have established that it is more likely than not that one of skill in the art would be convinced, to a reasonable probability, that the PRO539 protein is overexpressed in certain cancers, and therefore

antibodies to PRO539 have utility as a diagnostic tool. To the extent that the enablement rejection is based on a lack of utility, Applicants respectfully request that the Examiner reconsider and withdraw the enablement rejection under 35 U.S.C. §112.

As to the Examiner's recitation of the *In re Wands* factors, Applicants note that the question of enablement regarding antibodies is the very issue that was addressed in *In re Wands*, 858 F.2d 731, 8 U.S.P.Q. 2d 1400 (Fed. Cir. 1988). In *Wands*, the CAFC held that the disclosure was sufficient to enable one of skill in the art to make monoclonal antibodies to a disclosed antigen without undue experimentation. *Id.* at 740. If the disclosure was sufficient at the time of filing of the *Wands* application in 1980, it cannot be that the art of making antibodies has become less predictable in the ensuing 25 years, and now requires undue experimentation.

In addition, Applicants submit that the specification discloses how to make and use the claimed antibodies. For example, Example 27 on page 127 of the specification specifically describes the preparation of antibodies that bind PRO polypeptides. *Specification* at 90, line 20 through 97, line 4, and 127, line 13, through 128, line 1. The specification also discloses that the claimed antibodies can be used in diagnostic assays to detect the expression of PRO539 in specific types of tissue. *Specification* at 98, lines 5-29.

Therefore, given the teaching in the specification on how to make and use the claimed antibodies to detect expression of PRO539 in specific tissues, one of skill in the art would be enabled to practice the claimed invention without undue experimentation. Thus, at least one use of antibodies to the PRO539 polypeptide is adequately enabled, which is all that is required – "if any use is enabled when multiple uses are disclosed, the application is enabling for the claimed invention." *M.P.E.P.* § 2164.01(c). In view of the above, Applicants respectfully request that the Examiner reconsider and withdraw the enablement rejection under 35 U.S.C. § 112, first paragraph.

CONCLUSION

In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: March 16, 2007

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